Amendments to the Drawings:

Attached hereto, as Exhibit 1 of this Response, is a Replacement Sheet of drawings including changes to Figure 1, and replaces the original sheet including Figure 1. An Annotated Sheet showing the changes to Figure 1 is also included at Exhibit 1.

Specifically, Figure 1 has been amended as shown on the included Annotated Sheet to recited lengths of AdE1A and AdE1B that correspond to the E1A and E1B nucleotide sequences set forth in SEQ ID NOS:1 and 2, respectively; *i.e.*, 899 and 1823 base pairs instead of 911 and 1836 base pairs. The changes do not introduce new matter.

REMARKS

Status of the Claims

Claims 4-21 are currently pending and under consideration in this application. The foregoing amendments are limited to the cancelation of claims 4-7 and 12, without admission and without prejudice to Applicants' right to pursue the subject matter of those canceled claims either in this or other (*e.g.*, related divisional and/or other continuing) applications. Hence, claims 8-11 and 13-21 will be pending and under consideration upon the entry of this amendment.

The foregoing amendment is limited to the cancelation of claims (without prejudice or admission), and is therefore compliant with the requirements of 37 C.F.R. §116(b)(1) for amendments after a final Office Action. No new matter has been introduced. Entry and consideration of the foregoing amendment is therefore respectfully requested.

The Objections to the Claims Under 37 C.F.R. § 1.75 Should Be Withdrawn:

The Examiner has objected to claims 13-16 and 21 as being substantial duplicates of claims 4-7 and 12, respectively. In particular, the Examiner has taken the position that the phrases "capable of replicating in a local cancer area" (in independent claim 4) and "capable of replicating in a cancer cell" (in independent claims 13) are inherent characteristics that do not impart any structural difference of the "polynucleotide cassette" recited in either claim. Without commenting on or admitting to the propriety of these arguments, Applicants note that claims 4-7 and 12 have been canceled, *supra*, without prejudice or admission. Hence, the Examiner's objection to claims 13-16 and 21 as duplicative of those canceled claims has been obviated. Applicants therefore respectfully request that the objection under 37 C.F.R. § 1.75 be withdrawn.

The Rejection for Indefiniteness Under 37 C.F.R. § 112, Second Paragraph, Should Be Withdrawn:

The Examiner has rejected the pending claims under the second paragraph of 35 U.S.C. § 112, as being indefinite. In particular, the Examiner has taken the position that the sequences recited for E1A (SEQ ID NO:1) and E1B (SEQ ID NO:2) differ from the lengths indicated in

Figure 1 for those genes, and that these "discrepancies" render the claims unclear regarding exactly what nucleotide sequences are included in E1A and E1B recited in the independent claims.

Without commenting on or admitting to the propriety of the Examiner's position, Applicants note that Figure 1 has been amended, to indicate lengths for the genes ADE1A and ADE1B that are consistent with the lengths of SEQ ID NO:1 and SEQ ID NO:2 – namely 899 and 1823 base pairs, respectively. It is therefore believed that the rejection for indefiniteness has been obviated, and should be withdrawn.

The Prior Art Rejections Should Be Withdrawn

Applicants note, with appreciation, that the previous rejections of the pending claims under 35 U.S.C. § 103(a) as unpatentable over International Publication No. WO 2000/46355 by Morin *et al.* ("Morin") in view of Li *et al.*, *Cancer Res.* (2001) 61(17):6428-36 ("Li"); U.S. Patent Publication No. 2003/0104625 by Cheng *et al.* ("Cheng"); and/or U.S. Patent No. 6,692,736 to Yu *et al.* ("Yu") have all been withdrawn. However, the Examiner has made new rejections of the pending claims under 35 U.S.C. § 103(a), as being unpatentable over the Morin publication in view of either Li or Yu, *supra*, in further view of the following publications:

- WO 2002/20754 by Stuart *et al.* ("Stuart");
- WO 2000/42208 by Nemerow *et al.* ("Nemerow");
- WO 2000/40741 by Arya ("Arya"); and
- WO 1999/339988 by Hagen *et al.* (the "Hagen PCT publication").[1]

Specifically, the Morin publication is said to describe an oncolytic virus where an hTERT promoter element is used to control expression of a toxin or a genetic element essential for viral replication, to direct selective expression and/or viral replication in cancer cells. The Examiner acknowledges that Morin does not describe any adenovirus where IRES is inserted between E1A

[1] Applicants note that Hagen in a German language PCT publication. However, Canadian patent publication no. CA 2 316 282 A1 (the "Hagen CA publication") indicates, on its face, that it corresponds to the Hagen PCT publication. Accordingly, Applicants have relied on the Hagen CA publication as an English language translation of the Hagen PCT publication disclosure. For the Examiner's convenience, a copy of the Hagen CA publication is attached to this Response, as Exhibit 2.

and E1B genes, but argues that the Li and Yu publications describe adenovirus constructs where E1A-IRES-E1B are operably linked to a selective promoter, as well as administration of those constructs to cancer cells. With respect to the specific E1A, E1B, IRES and hTERT sequences recited in the independent claims (*i.e.*, SEQ ID NOS:1-4, respectively), the Examiner acknowledges that these also are not described by Morin. However, the Stuart, Nemero, Arya and Hagen publications are said to disclose nucleotide sequences that are 100% identical to to each of SEQ ID NOS:1-4, respectively. From this, the Examiner concludes that the recited nucleotide sequences of E1A, E1B, IRES and hTERT were well known in the art, and that it would have been obvious to combine those sequences with the teachings of Morin and Li and/or Yu to derive the presently claimed invention.

Applicants respectfully traverse these new rejections and submit that they should also be withdrawn. Applicants respectfully submit that the Examiner is mistaken when (s)he concluedes that the Stuart, Nemerow, Arya and Hagen publications establish that any of the E1A (SEQ ID NO:1), E1B (SEQ ID NO:2), IRES (SEQ ID NO:3) or hTERT (SEQ ID NO:4) nucleotide sequences recited in the pending claims were well known in the art. Hence, a skilled person would not have known and could not have used those sequences as called for in the presently claimed invention. This is explained below with respect to each publication cited in the Office Action.

A. Stuart Does Not Disclose the Nucleotide Sequence of E1A

Turning, first, to the publication of Stuart *et al.* (WO 2002/20754), the Office Action provides, on pages 12-13, what Applicants understand is an alignment of Stuart's SEQ ID NO:45 and SEQ ID NO:1 of the instant application. This alignment indicates a 100.0% match between nucleotides 1-899 of Applicants' SEQ ID NO:1 and nucleotides 282-1180 of Stuart's SEQ ID NO:45. However, Stuart's SEQ ID NO:45 is just one of some 275 cDNA sequences that Stuart allegedly derived from human tissues and cell lines, and assembled into "consensus" or "template" sequences. *See* Stuart at lines 29-36 on page 124. In Table 2 on page 185 of that publication, Stuart indicates that its SEQ ID NO:45 corresponds, at least in some parts, to "Homo sapiens chromosome 13, partial sequence and human adenovirus type 5 E1A nucleoprotein gene, partial cds." But Stuart does not identify the specific nucleotides shown in the Examiner's

alignment. To the contrary, Stuart's Table 3 indicates, on page 198, that "early E1A" protein is encoded by nucleotides 285-1151 of its SEQ ID NO:45. Hence, Stuart does not teach or suggest an "E1A gene consist[ing] of the nucleotide sequence of SEQ 1D NO:1" as recited in the pending independent claims of this application. In fact, by teaching that the "early E1A protein" is actually encoded by a different sequence of nucleotides, Stuart actually teaches *away* from the E1A gene recited in Applicants' pending claims.

B. Nemerow Does Not Disclose the Nucleotide Sequence of E1B

The Office Action provides an alignment of SEQ ID NO:2 of the instant application and a GRE5-E1-SV40-Hygro" plasmid sequence from Nemerow *et al.* (WO 2000/42208) at pages 14-16,[2] and indicates that nucleotides 1-1823 of Applicants' SEQ 1D NO:2 are 100.0% identical to nucleotides 2123-3945 of Nemerow's GRE5-E1-SV40-Hygro plasmid. However, Nemerow does not teach or even suggest that its GRE5-E1-SV40-Hygro plasmid might contain an E1B gene, let alone identify nucleotides 2123-3945 as corresponding to such a gene. Hence, a skilled person reading Nemerow would not be able to identify in that publication any "E1B gene consist[ing] of the nucleotide sequence of SEQ 1D NO2" as recited in the pending independent claims of this application.

C. Arya Does Not Disclose the Nucleotide Sequence of IRES

An alignment of Applicants' SEQ ID NO:3 and a "PSGT5 (SDM/RRE1/CM) backbone transfer vector" sequence from Arya (WO 2000/40741) is presented at pages 17-18 of the Office Action.[3] The alignment indicates that nucleotides 1-605 of Applicants' SEQ 1D NO:3 and 341-945 of Arya's PSGT5 (SDM/RRE1/CM) backbone transfer vector are 100.0% identical. Yet Arya does not even teach or suggest that its PSGT5 (SDM/RRE1/CM) backbone transfer vector contains an IRES sequence, let alone identify nucleotides 341-945 as corresponding to such a sequence. Hence, Arya does not teach or suggest any "IRES sequence consist[ing] of the nucleotide sequence of SEQ ID NO:3" as called for in the pending independent claims of this application.

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[2] Although the Office Action does not specify, this appears to be SEQ ID NO:48 of Nemerow. See in particular at page 77, lines 16-17 of Nemerow.

[3] Again, the Office Action does not specify. However, this appears to be SEQ ID NO:31 of Arya. *See* Arya at page 8, lines 21-22.

D. Hagen Does Not Disclose the Nucleotide Sequence of hTERT

Finally, Applicants turn to the alignment of SEQ ID NO:4 in this application and SEQ ID NO:1 of Hagen *et al.* (WO 99/33998) shown at pages 19-20 of the Office Action. The alignment indicates at nucleotides 1-455 of Applicants' SEQ ID NO:4 align with and are 100.0% identical to nucleotides 4669-5123 of Hagen's SEQ ID NO:1. However, Hagen only discloses that its SEQ ID NO:1 corresponds to "the 5'-flanking regulatory DNA sequence" of a human gene encoding a catalytic telomerase subunit. *See* the Hagen CA publication (Exhibit 2) at page 6, lines 5-10. Hagen does not say or indicate any specific portion that might be used as a promoter element in a genetic construct; let alone a portion that corresponding to "the hTERT promoter consist[ing] of the nucleotide sequence of SEQ ID NO:4" recited in the pending independent claims of this application.

E. The Use of SEQ ID NOS:1-4 Is Not* Prima Facie *Obvious

Hence, contrary to what is stated in the Official Action, the cited publications of Stuart, Nemerow, Arya and Hagen do *not* teach or describe the specific E1A, E1B, IRES or hTERT nucleotide sequences of the present invention. At best these publications only describe base sequences that may contain the nucleotide sequences of Applicants' SEQ ID NOS:1-4. However, there is not teaching or suggestion in any of the cited references to indicate which nucleotides in those base sequences may correspond to E1A, E1B, IRES or hTERT; let alone any teaching leading a skilled person to select specific subsequences corresponding to SEQ ID NOS:1-4 in the currently pending claims.

The Examiner indicates that the U.S. Supreme Court decision of *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007) forecloses the argument that a specific teaching, suggestion or motivation is required to support the rejection for obviousness. However, the Supreme Court acknowledged, in *KSR*, "the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus. V. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007), *quoting KSR*, 550 U.S. at 418. Hence, the U.S. Court of Appeals for the Federal Circuit has maintained, even after *KSR*, that it is still necessary to identify some reason that would have a led a person of ordinary skill in the art to modify the

prior art in a particular manner to establish *prima facie* obviousness. *See* for example, in *Takeda Chem. Indus.*, 492 F.3d at 1357. As explained above, there is no reason for a skilled person to select specific portions of the full length sequences in the prior art, to use as E1A, E1B, IRES or hTERT sequences in a construct of the presently claimed invention. For these reasons alone, Applicants respectfully submit that the claimed invention can not be *prima facie* obvious or unpatentable under 35 U.S.C. § 103(a).

F. The Fjuiwara Declaration Rebuts Any Finding of* Prima Facie *Obviousness

In addition to the foregoing, Applicants respectfully direct the Examiner's attention to the Declaration of the inventor Toshiyoshi Fujiwara under 37 C.F.R. § 1.132 submitted on November 4, 2009 in connection with this application. The declaration demonstrates the unpredictable effects of the claimed invention. In particular, data presented in the declaration show that local administration of a recombinant virus according to the invention (*i.e.*, Telomelysin) to three cancer patients caused at least 20% tumor shrinkage in the cancer of patients to whom it was administered without causing any serous side effects. The results show that a recombinant virus as recited in the pending claims is extremely effective in triggering tumor shrinkage without causing any serious side effects. In contrast, none of the references cited by the Examiner teaches or suggests that, when a recombinant virus is administered to human subject, it will similarly affect tumor shrinkage without triggering side effects. Hence, even if the invention were *prima facie* obviousness over the cited references, such obviousness must be rebutted, *e.g.*, by the unpredictable and, hence, unexpected results presented in the Fujiwara Declaration.

For at least the foregoing reasons, Applicants respectfully submit that the rejections under 35 U.S.C. § 103(a) should be withdrawn.

Conclusion

For at least the foregoing reasons, Applicants respectfully submit that each of the outstanding objections and rejections to this application has been overcome and/or obviated. Accordingly, the withdrawal of all objections and rejections, and allowance of the pending claims are all respectfully requested. The Examiner is moreover invited to contact Applicants'

undersigned representative(s) should the (s)he conclude that there are additional issues that could be readily resolved, *e.g.*, in an interview of by Examiner's amendment. An allowance is earnestly sought..

Respectfully submitted,

Date: April 20, 2010

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Attachment:

- Exhibit 1: Replacement and Annotated Sheets with changes to Figure 1
- Exhibit 2: Canadian patent publication no. CA 2 316 282 A1 (the "Hagen CA publication")

EXHIBIT 1